Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants

Rachel L. Peters, MPH,[a,b] Katrina J. Allen, BMedSc, MBBS, FRACP, FAAAAI, PhD,[a,b,c] Shyamali C. Dharmage, MBBS, MSc, MD, PhD,[a,d] Mimi L. K. Tang, MBBS, FRACP, FRCPA, PhD,[a,b,c] Jennifer J. Koplin, PhD,[a,b] Anne-Louise Ponsonby, BMedSci, MBBS, PhD,[a,b,d] Adrian J. Lowe, PhD,[a,d] David Hill, MBBD, FRACP,[a] and Lyle C. Gurrin, PhD,[a,d] for the HealthNuts study *Melbourne, Australia*

Background: Ninety-five percent positive predictive values (PPVs) provide an invaluable tool for clinicians to avoid unnecessary oral food challenges. However, 95% PPVs specific to infants, the age group most likely to present for diagnosis of food allergy, are limited.

Objective: We sought to develop skin prick test (SPT) and allergen-specific IgE (sIgE) thresholds with 95% PPVs for challenge-confirmed food allergy in a large population-based cohort of 1-year-old infants with challenges undertaken irrespective of SPT wheal size or previous history of ingestion.

Methods: HealthNuts is a population-based, longitudinal food allergy study with baseline recruitment of 1-year-old infants. Infants were recruited from council-run immunization sessions during which they underwent SPTs to 4 allergens: egg, peanut, sesame, and cow's milk/shrimp. Any infant with a detectable SPT response was invited to undergo oral food challenge and sIgE testing.

Results: Five thousand two hundred seventy-six infants participated in the study. Peanut SPT responses of 8 mm or greater (95% CI, 7-9 mm), egg SPT responses of 4 mm or greater (95% CI, 3-5 mm), and sesame SPT responses of 8 mm or greater (95% CI, 5-9 mm) had 95% PPVs for challenge-proved food allergy. Peanut sIgE levels of 34 kU_A/L or greater (95% CI, 14-48 kU_A/L) and egg sIgE levels of 1.7 kU_A/L or greater (95% CI, 1-3 kU_A/L) had 95% PPVs for challenge-proved food allergy. Results were robust when stratified on established risk factors for food allergy. Egg SPT responses and sIgE levels were poor predictors of allergy to egg in baked goods.

Conclusion: These 95% PPVs, which were generated from a unique dataset, are valuable for the diagnosis of food allergy in young infants and were robust when stratified across a number of different risk factors. (J Allergy Clin Immunol 2013;132:874-80.)

Key words: *Food allergy, skin prick test, serum-specific IgE, oral food challenge, predictive value of tests, egg, baked egg, peanut, sesame*

IgE antibody levels, as determined based on either skin prick test (SPT) responses or serum allergen-specific IgE (sIgE) levels, are poorly correlated with the gold standard test for food allergy: the oral food challenge (OFC). Therefore 95% positive predictive values (PPVs) have been developed as a surrogate for the OFC and to minimize both overdiagnosis of food allergy by relying on SPT responses or sIgE levels alone and unnecessary, labor-intensive, and potentially dangerous OFCs.[1,2]

SPT and sIgE 95% PPV thresholds have been reported to be dependent on age, with infants more likely to have lower 95% PPVs than children older than 2 years.[3,4] However IgE-mediated food allergy is most likely to present for diagnosis in the first 2 years of life.[5] To date, there has been a paucity of data on 95% PPVs in this age group. Recently, it has been found that PPVs derived from clinic populations cannot be meaningfully applied to general populations, highlighting the need for population-based PPVs.[6]

The association between SPT responses or sIgE levels and the risk of challenge-confirmed food allergy has not previously been examined in a population sample of 1-year-old infants. Nor have challenges been undertaken systematically in infants with detectable SPT responses, irrespective of the magnitude of wheal size or previous history of ingestion with predetermined, objective stopping criteria.

We aimed to examine the diagnostic value of SPT responses and sIgE levels to challenge-confirmed food allergy in 1-year-old infants recruited from a population-based sample and to develop thresholds above which an infant is highly likely to have food allergy. In addition, we aimed to establish whether these

From [a]the Murdoch Childrens Research Institute; [b]the Department of Paediatrics, University of Melbourne; [c]the Department of Allergy and Immunology, Royal Children's Hospital; and [d]the Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, University of Melbourne.

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Corresponding author: Katrina J. Allen, BMedSc, MBBS, FRACP, FAAAAI, PhD, Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Rd, Parkville 3052, Victoria, Australia. E-mail: katie.allen@rch.org.au.

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Abbreviations used
AUC: Area under the curve
LR: Likelihood ratio
NPV: Negative predictive value
OFC: Oral food challenge
PPV: Positive predictive value
ROC: Receiver operating characteristic
sIgE: Allergen-specific IgE
SPT: Skin prick test

thresholds with 95% PPVs for food allergy were different when stratified by known risk factors for food allergy, including infantile eczema, previous reaction history, sex, vitamin D levels, and family history of allergic disease.

METHODS

Study design

The HealthNuts study is a population-based, longitudinal food allergy study in Melbourne, Australia. The study methods have been described in detail previously.[7] In brief, 5276 infants aged 11 to 15 months were recruited through 131 council-run immunization sessions from September 2007 to August 2011. Infants underwent SPTs to 4 common food allergens, and infants with detectable SPT responses were invited to Melbourne's Royal Children's Hospital for a formal OFC to test for food allergy. Infants with a negative SPT response in the presence of a positive histamine control were considered highly unlikely to have IgE-mediated allergy to these foods and did not undergo OFCs. To validate this assumption, we undertook OFCs in 200 randomly selected SPT negative controls. None had a positive OFC result in the context of negative SPT responses and were subsequently excluded from this analysis. Nurses were blinded to wheal size and previous history of ingestion.

SPT

SPTs were administered with a single-tine lancet (Stallergenes, Antony, France) on the infant's back. Tests were performed to 4 foods, peanut, hen's egg, sesame, and either cow's milk or shrimp (ALK-Abelló, Madrid, Spain), along with a positive control (10 mg/mL histamine) and a negative control (saline). Wheal size was measured after 15 minutes and calculated as the average of the longest diameter and the diameter perpendicular to it after subtracting the negative control.

Serum-specific IgE testing

Blood samples were collected and plasma was isolated for sIgE assays on the same day. Serum specific IgE antibodies to whole peanut, egg white, and sesame were analyzed by using the ImmunoCAP System FEIA (Phadia AB, Uppsala, Sweden).

OFCs

Eighty-three percent of infants with detectable SPT responses at community recruitment accepted the invitation to undergo an OFC. SPTs were repeated on the day of the OFC and used for this analysis; OFCs were conducted as previously described.[7] OFC results were deemed positive if they met the predefined criteria (see definitions) within 2 hours of the last challenge dose. To capture late reactions, parents were instructed to administer a single serving of the challenge food for 7 days and observe for a reaction. The food challenge result was deemed negative if the infant tolerated the top dose of the challenge and did not report a late reaction after consumption of the top challenge dose at home for 1 week or if the infant's parent reported that the infant was regularly consuming and tolerating the food after a negative OFC result. Food challenges were deemed inconclusive and the parents were offered a repeat challenge if the infant refused to ingest the challenge food at the clinic or if the parent reported a late reaction that did not meet the positive challenge criteria yet led the parent to remove the food from the infant's diet. In addition, positive OFC results in infants without any evidence of IgE sensitization to the allergen were also considered inconclusive.

A subset of infants with positive test results to raw egg white were also offered a baked egg challenge (n = 185). Recruitment for baked egg challenges began partway through the study, and all infants who had challenge-confirmed allergy to raw egg white were offered an OFC to baked egg in the form of a muffin. Data from baked egg challenges are therefore derived from a consecutive series of infants who had challenge-confirmed raw egg allergy.

Ethics

Ethics approval was obtained for the HealthNuts study from the Victorian State Government Office for Children (reference no. CDF/07/492), the Victorian State Government Department of Human Services (reference no. 10/07), and the Royal Children's Hospital Human Research Ethics Committee (reference no. 27047).

Statistical methods

The diagnostic capacity of tests for food allergy was assessed by using receiver operating characteristic (ROC) curves; the area under the curve (AUC) was calculated to quantify the accuracy of the test. Logistic regression was used to model the association between the risk of food allergy and the measure of sensitization (either SPT wheal size or sIgE threshold) by assuming a linear relationship between the log of the proportion of patients with food allergy and the numeric measure of sensitization. A fitted probability of food allergy was produced for each participant given their SPT wheal size or sIgE threshold, and these were used to replace the observed binary outcome in the standard formula for the PPV; that is, a modeled PPV for each level of SPT wheal size or sIgE threshold was produced by taking the average of the fitted probability of food allergy for all infants with an SPT wheal size or sIgE threshold of greater than the given level. This method produces a smooth nondecreasing curve for the PPV across the range of SPT wheal sizes and sIgE thresholds. Therefore it overcomes fluctuations (sampling variation) in the observed proportions of infants with food allergy for increasing SPT responses and sIgE levels. To quantify the precision of estimation of the PPVs, we used bootstrapping, a method of deriving SEs and CIs from repeated samples drawn with replacement from the original dataset. Twenty bootstrap replications were used to determine the variability of parameter estimates and to calculate 95% CIs for the thresholds with 95% PPVs to food allergy.

Sensitivity, specificity, negative predictive value (NPV), and positive and negative likelihood ratios (LRs) were calculated for the thresholds that had 95% PPVs to food allergy. Note that these estimates of sensitivity and specificity pertain to the subpopulation who are SPT sensitized and not the general population of all infants. These estimates are still population based because the sample includes all SPT-sensitized infants and not just those with additional symptoms or a history or clinical indication of increased allergic risk, as would be typical of an allergy clinic at a tertiary referral hospital. Data from inconclusive challenges were excluded from the analysis.

The analysis was stratified on known risk factors for food allergy: sex, eczema, vitamin D insufficiency, previous reaction history, and family history of allergic disease or food allergy. Stratum-specific 95% PPV thresholds were compared with the z test. STATA release 12.0 (StataCorp, College Station, Tex) was used for all analyses.

Definitions

Sensitization was defined as an SPT response of 2 mm or greater or an sIgE levels of 0.35 kU_A/L or greater.

A positive OFC result was defined as at least 1 of the following: 3 concurrent non–contact urticaria reactions lasting at least 5 minutes, severe persistent vomiting, perioral or periorbital angioedema, or anaphylaxis (evidence of circulatory or respiratory involvement) within 2 hours of the last challenge dose in the presence of a positive test result for sensitization.

Eczema was defined as a parent-reported doctor's diagnosis of eczema.